

DETAILED ACTION

Status of the Application

Claims 1-17 and 19-29 are pending.

It is noted that the examination of the instant application has been assigned to a different Examiner in Group Art Unit 1652.

Applicant's election without traverse of Group I, claims 1-7, 26 drawn to a protein having the activity of degrading a dsRNA, and a composition comprising a protein having the activity of degrading a dsRNA and binding to a nucleic acid, as submitted in a communication filed on 4/7/2008, is acknowledged.

Upon further consideration, the current Examiner will rejoin claims 10 and 27 for examination on the merits. Claims 10 and 27 are directed to kits comprising the protein of claims 1 and 26, respectively. Since a kit comprising said proteins is essentially a product comprising the elected protein, a kit as claimed is deemed an obvious variation of the elected invention. Therefore, the restriction requirement among Inventions I, IV and VII as set forth in the restriction requirement mailed on 3/5/2008 is hereby withdrawn.

Claims 8-9, 11-17, 19-25, 28 and 29 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Claims 1-7, 10, 26-27 are at issue and are being examined herein.

It is noted that claims 26-27 are generic and are directed to a composition/kit comprising a protein having dsRNA degrading activity and a protein having nucleic acid binding activity. As written, the claims encompass compositions/kits where the activities recited (dsRNA degrading and nucleic acid binding activities) can be found in a single polypeptide. If the claims are later amended to recite specific non-obvious combinations of proteins, such that the recited activities are in different specific polypeptides, the Examiner may issue a supplemental restriction requirement for the combinations.

Specification

1. The preliminary amendments to the specification filed on 2/10/2006 and 3/12/2007 are acknowledged.
2. The abstract of the specification is objected to as it contains improper idiomatic English. See, for example, “a dsRNA in the coexistence of a protein having an activity...”, “to elevate the efficiency in an RNA synthesis reaction typified by dsRNA synthesis”. Appropriate correction is required.
3. The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. In the instant case, the claims are directed to a protein, whereas the title refers to a method. Appropriate correction is required.

Priority

4. Acknowledgment is made of a claim for foreign priority under 35 U.S.C. 119(a)-(d) to JAPAN 2003-293553 filed on 08/14/2003, JAPAN 2003-342126 filed on 09/30/2003, JAPAN 2003-409639 filed on 12/08/2003 and JAPAN 2004-086129 filed on 03/24/2004. No certified English translation of these documents have been submitted.
5. This application has been filed as the US national stage of PCT/JP04/11480 on 08/10/2004.

Information Disclosure Statement

6. The information disclosure statements (IDS) submitted on 4/15/2008, 10/10/2006 and 5/9/2006 are acknowledged. The submissions are in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statements are being considered by the examiner.

Claim Objections

7. Claim 1 (claims 2-5, 7, 10 dependent thereon) is objected to due to the recitation of "A protein having an activity of degrading dsRNA, which has an activity of acting on a dsRNA to produce a dsRNA of a specific length". To avoid redundancy, it is suggested the term be amended to recite, for example, "A protein which has an activity of acting on a dsRNA to produce a dsRNA of a specific length".

Appropriate correction is required.

8. Claim 7 is objected to due to the recitation of "in which one or plural amino acid(s) is (are) substituted..". For consistency with commonly used claim language, it is suggested the term be amended to recite "in which one or several amino acids are substituted...". Appropriate correction is required.

9. Claim 10 is objected to due to the recitation of "a kit comprising the protein having....defined by claim 1". To be consistent with commonly used claim language, it is suggested the term be amended to recite "a kit comprising the protein of claim 1". Appropriate correction is required.

10. Claims 26-27 are objected to due to the recitation of "used for the method defined by claim 11". The claims depend upon a non-elected claim. For examination purposes, no patentable weight will be given to the term. Appropriate correction is required.

Claim Rejections - 35 USC § 101

11. 35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

12. Claims 1-7 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

13. Claims 1-7, as written, do not sufficiently distinguish over proteins as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of the hand of man, the naturally occurring

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products are considered non-statutory subject matter. See *Diamond v. Chakrabarty*, 447 US 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of “isolated” or “purified” as taught by Example 4 of the specification. See MPEP 2105.

Claim Rejections - 35 USC § 112, Second Paragraph

14. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

15. Claims 3-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

16. Claim 3 (claim 4 dependent thereon) is indefinite in the recitation of “consists of RNase IIIa, RNase IIIb...” for the following reasons. The terms “RNase IIIa” and “RNase IIIb” are being recited in a generic fashion, i.e., they are not limited to any source or to a particular polypeptide. While one of skill in the art would recognize what the term “RNase domain” is, one of skill in the art would not recognize what an RNase IIIa or IIIb domain is since neither the art nor the specification provide the specific biological activity/structural characteristics associated with an RNase IIIa or RNase IIIb domain which set them apart from other RNase III domains, or other characteristics which are unique to an RNase IIIa or IIIb domain such that one could clearly distinguish an RNase IIIa or IIIb domain from other RNase III domains. In the absence of a definition of the characteristics (functional and/or structural) associated with the terms “RNase IIIa” and “RNase IIIb”, one of skill in the art cannot reasonably apprised of the scope of the invention. For examination purposes, the terms “RNase IIIa” and “RNase IIIb” will be interpreted as “RNase III”. If the intended meaning is two RNase III domains, it is suggested the claim be amended to recite, for example, “two RNase III domains and a dsRNA domain”. Correction is required.

17. Claim 4 is indefinite in the recitation of “the protein according to claim 3 which further contains a PAZ domain” for the following reasons. Claim 3, from which claim 4 depends, defines the genus of

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domains to three domains only, due to the recitation of the term "consists". Therefore, claim 4 is a broader claim than the claim from which it depends as it requires an additional domain, i.e., PAZ. For examination purposes, it will be assumed that claim 3 recites "wherein the protein comprises two RNA III domains and a dsRNA binding domains". Correction is required.

Claim Rejections - 35 USC § 112, First Paragraph

18. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

19. Claims 1-5, 7, 10, 26-27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1-5, 7 and 10 encompass a genus of proteins comprising any structure (i.e., sequence), wherein said proteins have dsRNA degrading activity. Claims 26-27 are directed to compositions/kits comprising a genus of proteins having dsRNA degrading activity and a genus of proteins having nucleic acid binding activity, wherein the proteins in both genera can have any structure. It should be noted that since claim 7 allows for any number of modifications in the polypeptides of SEQ ID NO: 4 or 17, the structures of the proteins recited in claim 7 are essentially undefined. Also, while claims 2-4 refer to specific domains, the claims do not specify any structure for these domains. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation.

In *University of California v. Eli Lilly & Co.*, 43 USPQ2d 1938, the Court of Appeals for the Federal Circuit has held that "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or]

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chemical name,' of the claimed subject matter sufficient to distinguish it from other materials". As indicated in MPEP § 2163, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show that Applicant was in possession of the claimed genus. In addition, MPEP § 2163 states that a representative number of species means that the species which are adequately described are representative of the entire genus. Thus, when there is substantial variation within the genus, one must describe a sufficient variety of species to reflect the variation within the genus.

There is no actual structural limitation with regard to the members of the genus of proteins recited. While the specification in the instant application discloses the structure of two fragments of a single DICER polypeptide, i.e., SEQ ID NO: 4 and 17 are fragments of the DICER polypeptide of SEQ ID NO: 1, it provides no clue as to the structural elements required in any protein having dsRNA degrading activity wherein said protein degrades dsRNA in fragments of 15 to 30 base pairs in length, nor does it teach which structural elements within the polypeptide of SEQ ID NO: 1, or the fragments of SEQ ID NO: 4/17, are required in any protein having the recited dsRNA degrading activity. Furthermore, the specification is silent with regard to the structural features required in any DICER protein, any RNase III domain, any PAZ domain, or any dsRNA binding domain. It should be noted that DICER proteins known in the art are extremely large proteins (over 1000 amino acids). Thus, even if some motifs associated with RNase III, PAZ and dsRNA binding domains are known, these motifs are not considered substantially large such that they define a significant portion of a DICER protein, or a substantial portion of a domain of a DICER protein.

The claim encompass a large genus of proteins which is structurally unrelated. A sufficient written description of a genus of polypeptides may be achieved by a recitation of a representative number of polypeptides defined by their amino acid sequence or a recitation of structural features common to members of the genus, which features constitute a substantial portion of the genus. However, in the instant case, there is no structural feature which is representative of all the members of the genus of proteins recited in the claims, and there is no information as to a correlation between structure and function. Furthermore, while one could argue that SEQ ID NO: 4 or 17 are representative of the structure of all the members of the genus, such that the recited genus of polypeptides is adequately described, it is noted that the art teaches several examples of how even small changes in structure can lead to changes in enzymatic function. For example, Witkowski et al. (Biochemistry 38:11643-11650, 1999) teach that one conservative amino acid substitution transforms a β -ketoacyl synthase into a malonyl decarboxylase and completely eliminates β -ketoacyl synthase activity. Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) teach that two naturally occurring *Pseudomonas* enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, thus having different function. Therefore, since minor structural changes to a polypeptide may result in changes affecting function, and no additional information correlating structure with the recited activity has been provided, one cannot reasonably conclude that the fragments of SEQ ID NO: 4 or 17, or the DICER protein of SEQ ID NO: 1 are representative of the structure of all proteins having the dsRNA degrading activity as claimed.

Due to the fact that the specification only discloses a single DICER protein and two fragments of said protein, and the lack of description of any additional species by any relevant, identifying characteristics or properties, one of skill in the art would not recognize from the disclosure that Applicant was in possession of the claimed invention.

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20. Claims 1-5, 7, 10, 26-27 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a protein comprising/consisting of SEQ ID NO: 4 or 7, does not reasonably provide enablement for (1) a protein having any structure and dsRNA degrading activity, (2) a protein having dsRNA degrading activity wherein said protein can have any RNase III and dsRNA binding domains, (3) a composition/kit comprising the proteins of (1) or (2), or (4) a composition/kit comprising the protein of (1) and a protein comprising any structure wherein said protein can bind to any nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required are summarized in *In re Wands* (858 F.2d 731, 737, 8 USPQ2d 1400 (Fed. Cir. 1988)) as follows: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breadth of the claims. The factors which have lead the Examiner to conclude that the specification fails to teach how to make and/or use the claimed invention without undue experimentation, are addressed in detail below.

The breadth of the claims. Claims 1-5, 7, 10, 26-27 are so broad as to encompass (1) a protein having any structure and dsRNA degrading activity, (2) a protein having dsRNA degrading activity wherein said protein can have any RNase III and dsRNA binding domains, (3) a composition/kit comprising the proteins of (1) or (2), or (4) a composition/kit comprising the protein of (1) and a protein comprising any structure wherein said protein can bind to any nucleic acid. See Claim Rejections under 35 USC 112, second paragraph, for claim interpretation. The enablement provided is not commensurate in scope with the claims due to the extremely large number of proteins of unknown structure

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encompassed by the claims. In the instant case, the specification enables a protein comprising/consisting of SEQ ID NO: 4 or 7

The amount of direction or guidance presented and the existence of working examples. The specification discloses the amino acid sequence of a single DICER protein as a working example (SEQ ID NO: 1) and two enzymatically active fragments (SEQ ID NO: 4 and 17 degrade dsRNA). However, the specification fails to provide any clue as to the structural elements required in any protein having dsRNA degrading activity, or which are the structural elements in the polypeptides of SEQ ID NO: 1, 4 or 17 which are essential for any protein to display the desired dsRNA degrading activity. No correlation between structure and function has been presented. There is no information or guidance as to which amino acid residues in the polypeptides of SEQ ID NO: 4/17 can be modified and which ones are to be conserved to create a variant displaying the same activity as that of the polypeptide of SEQ ID NO: 4/17. There is no disclosure of the structural features associated with the ability to degrade dsRNA into fragments having the recited size. In addition, there is no information in the specification or the prior art regarding the structural features required in any nucleic acid binding domain such that when combined with a protein having dsRNA degrading activity, it can degrade dsRNA into fragments of a particular length.

The state of prior art, the relative skill of those in the art, and the predictability or unpredictability of the art. The amino acid sequence of a polypeptide determines its structural and functional properties. While the art discloses a few DICER proteins and a few motifs associated with the different domains found in known DICER proteins, neither the specification nor the art provide a correlation between structure and dsRNA degrading activity such that one of skill in the art can envision the structure of any protein having the recited activity. In addition, the art does not provide any teaching or guidance as to (1) which changes can be made to the protein of SEQ ID NO: 1 or its fragments such that the resulting variants would display the same activity, or (2) the general tolerance of DICER

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proteins/proteins having dsRNA degrading activity to structural modifications and the extent of such tolerance. The art clearly teaches that modification of a protein's amino acid sequence to obtain the desired activity without any guidance/knowledge as to which amino acids in a protein are tolerant of modification and which ones are conserved is highly unpredictable. At the time of the invention there was a high level of unpredictability associated with altering a polypeptide sequence with an expectation that the polypeptide will maintain the desired activity. For example, Branden et al. (Introduction to Protein Structure, Garland Publishing Inc., New York, page 247) teach that (1) protein engineers are frequently surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes, (2) the often surprising results obtained by experiments where single mutations are made reveal how little is known about the rules of protein stability, and (3) the difficulties in designing *de novo* stable proteins with specific functions. The teachings of Branden et al. are further supported by the teachings of Witkowski et al. (Biochemistry 38:11643-11650, 1999) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001) already discussed above, where it is shown that even small amino acid changes result in enzymatic activity changes.

The quantity of experimentation required to practice the claimed invention based on the teachings of the specification. While methods of generating or isolating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the art to screen by a trial and error process for all polypeptides having the recited activity. Furthermore, in view of the absence of guidance as to the structural features required in any protein having a nucleic acid binding domain such that when combined with any protein having dsRNA degrading activity, one could obtain dsRNA fragments of an specified length, one of skill in the art would have to test an infinite number of combinations to determine which combination of proteins can be used to obtain the desired length. In the absence of (1) a rational and predictable scheme for modifying any residue in the polypeptides of SEQ ID NO: 4/17 such that the resulting variants would maintain the same dsRNA degrading activity, (2) some knowledge or guidance

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as to the structural features associated with the recited activity such that one could isolate/test only those most likely to have the desired activity, (3) some knowledge or guidance as to which nucleic acid domains can be combined with a protein having dsRNA degrading activity such that dsRNA fragments of a particular length can be obtained, and/or (4) a correlation between structure and the recited dsRNA degrading activity, one of skill in the art would have to test an essentially infinite number of proteins to determine which ones have the desired activity.

Therefore, taking into consideration the extremely broad scope of the claim, the lack of guidance, the amount of information provided, the lack of knowledge about a correlation between structure and the desired function, and the high degree of unpredictability of the prior art in regard to structural changes and their effect on function, one of ordinary skill in the art would have to go through the burden of undue experimentation in order to practice the claimed invention. Thus, Applicant has not provided sufficient guidance to enable one of ordinary skill in the art to make and use the invention in a manner reasonably correlated with the scope of the claims.

Claim Rejections - 35 USC § 102

21. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

22. Claims 1-5, 7, 10, 26-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Provost et al. (EMBO Journal 21(21):5864-5873, 2002; cited in the IDS). Claims 1-5 are directed in part to a protein that has dsRNA degrading activity, wherein said protein produces dsRNA molecules of about 15-30 base pairs, and wherein said protein comprises a PAZ domain, two RNase III domains and a dsRNA binding domain. Claim 7 is directed in part to a protein comprising SEQ ID NO: 4 or 17 wherein said protein

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further comprises additional amino acids since the claim encompasses adding amino acids to SEQ ID NO: 4/17. Claim 10 is directed to a kit comprising the protein of claim 1 as described above. Claim 26 is directed in part to a composition comprising a protein, wherein said protein has both the activity of binding to a nucleic acid and the activity of degrading dsRNA. Claim 27 is directed in part to a kit comprising a protein, wherein said protein has both the activity of binding to a nucleic acid and the activity of degrading dsRNA. Neither claim 26 nor claim 27 require that the activities recited be in separate polypeptides. See Claim Rejections under 35 USC 112, second paragraph for claim interpretation.

Provost et al. teach a human DICER polypeptide which is 1912 amino acids and comprises both SEQ ID NO: 4 (654 amino acids) and SEQ ID NO: 17 (1246 amino acids). See attached alignment provided for visualization purposes. SEQ ID NO: 17 comprises all of SEQ ID NO: 4. The polypeptide of Provost et al. comprise a PAZ domain, two RNase III domains, and a dsRNA binding domain (Figure 1; page 5865 right column, last paragraph). Provost et al. also teach that the DICER protein generated 21-23 nucleotide dsRNA products (page 5867, right column, dsRNase activity). Since Provost et al. teach compositions comprising purified human DICER as well as the buffers and conditions for carrying out the dsRNase assay, Provost et al. teach a kit comprising the DICER protein (pages 5871-5872, Materials and Methods). Therefore, the teachings of Provost et al. anticipate the instant claims as written.

Claim Rejections - 35 USC § 103

23. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

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24. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(c), (f) or (g) prior art under 35 U.S.C. 103(a).

25. Claim 6 is rejected under 35 U.S.C. 103(a) as being unpatentable over Provost et al. (EMBO Journal 21(21):5864-5873, 2002; cited in the IDS) in view of Zhang et al. (EMBO Journal 21(21):5875-5885, 2002; cited in the IDS). The teachings of Provost et al. have been discussed above. Zhang et al. also teach the polypeptide of Provost et al. and teach additional functional characterization of the DICER protein (Abstract). Neither Zhang et al. nor Provost et al. teach a polypeptide consisting of SEQ ID NO: 4 or 17.

Claim 6 is directed in part to a polypeptide consisting of SEQ ID NO: 4 or 17.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make fragments of the polypeptide of Provost et al. by deleting amino acids from the N-terminus, wherein said fragments comprise the RNase III and dsRNA binding domains, including those consisting of (1) amino acids 1259-1912 (SEQ ID NO: 4), or (2) amino acids 667-1912 (SEQ ID NO: 17) of the polypeptide of Provost et al. A person of ordinary skill in the art is motivated to make such limited number of fragments for further characterization of the protein since Provost et al. teach that DICER proteins from other species have dsRNA degrading activity even when the PAZ and binding domains are not present (page 5866, left column, lines 3-4; page 5871, right column, lines 1-2) and Zhang et al. teach that while the RNase III and binding domains are most likely to be involved in the degradation of dsRNA, the role of the other domains is unknown (page 5875, right column, last paragraph). One of ordinary skill

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in the art has a reasonable expectation of success at making fragments of the protein of Provost et al. comprising the RNase III and dsRNA binding domains since both Provost et al. and Zhang et al. teach the approximate location of those domains in the human DICER protein, such that one of skill in the art would have known which fragments had these domains. Therefore, the invention as a whole would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made.

Conclusion

26. No claim is in condition for allowance.
27. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PMR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).
28. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Delia M. Ramirez whose telephone number is (571) 272-0938. The examiner can normally be reached on Monday-Friday from 9:30:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Nashaat Nashed can be reached on (571) 272-0934. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

/Delia M. Ramirez/

Delia M. Ramirez, Ph.D.
Primary Patent Examiner
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